

Applicants note with appreciation the withdrawal of rejections under 35 U.S.C. § 112, second paragraph, as well as the recasting of the enablement rejection. In accordance with this statement, Applicants have assumed that claim 58 was not meant to be rejected under 35 U.S.C. § 112, first paragraph later in the Office Action. If the rejection of this claim was intentional, clarification is respectfully requested.

### ***Specification***

The specification remains objected to because of the alleged improper incorporation by reference. Although the Office Action addresses only that portion of Applicants' arguments that pertain to incorporation of that portion of WO 95/18856 that discusses hedgehog proteins, Applicants assert that the recitation in WO 95/18856 is sufficient to incorporate the *entirety* of WO 95/18856 into the specification. As such, *all* of WO 95/18856 is presumed to be a part of the present application; the part that has been added by amendment represents only that portion that is *essential* matter.

The Office Action cites *In re Hawkins* as a case in which a portion of a prior filing was incorporated by reference without reciting specific column or page numbers. However, this decision shows only that the incorporation in that case was permissible, and in no way indicates that the present incorporation is *impermissible*. Applicants need not conform to the Examiner's selection of a particularly narrow fact pattern to justify incorporation by reference. The Office Action has cited not a single case – nor are Applicants aware of any – that have denied incorporation by reference when the phrase “incorporated by reference” occurs in the specification in connection with a published document. Absent any such legal precedent for the Examiner's position, Applicants submit that the present objection is without legal merit and should be withdrawn.

The Office Action further cites *In re Argoudelis*, but this citation appears irrelevant to the question of incorporation by reference, and so will be discussed in the context of the enablement rejection below.

### ***Claim Objections***

Claim 74 is objected to as allegedly failing to further limit the subject matter of the claim upon which it depends. Applicants again point out that the response filed on August 23, 2001, in which claims 76-81 *as originally numbered* were cancelled, and claims 67-75 were renumbered 65-73 by Applicants. This amendment was filed with a Request for Continued Examination, and as such should have been entered in full. Nevertheless, Applicants hereby cancel claims 74 and 75 to the extent they are still considered pending.

***Claim Rejections – 35 U.S.C. §112, First Paragraph***

Claims 57-75 and 82-113 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection, as it is based entirely on an improper application of incorporation-by-reference doctrine as discussed in detail above. Reconsideration and withdrawal of this rejection are respectfully requested.

***Claims Rejections – 35 U.S.C. § 112***

Claims 57-75 and 82-113 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants maintain the arguments of record with regard to the enablement of the full scope of the claims. Nevertheless, to expedite prosecution, Applicants have amended the claims to more explicitly point out the hedgehog compounds for use in the subject methods. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The Office Action alleges that one of skill in the art would not have a reasonable expectation of success in practicing the claimed invention using hedgehog compounds other than naturally occurring hedgehog proteins. The Examiner cites Williams et al. to demonstrate that some hedgehog fragments may block hedgehog signal transduction. Applicants have amended the claims to more explicitly point out the functional characteristics of the hedgehog

polypeptides for use in the subject methods. Applicants contend that the claims are now explicitly limited to hedgehog compounds which not only bind patched, but are functionally equivalent to naturally occurring hedgehog proteins. Support for Applicants' amendment is found on page 21, lines 20-24 and page 22, lines 9-25.

The enablement of claims directed to the use of naturally occurring hedgehog polypeptides in the subject methods is not in question. Accordingly, Applicants contend that the claims, as amended, are explicitly limited to hedgehog polypeptides which are functionally equivalent to said naturally occurring hedgehog polypeptides. Applicants have explicitly excluded from the scope of the claims variants of hedgehog polypeptides which possess a different function such as the peptide fragments taught by Williams et al.

The amended claims are explicitly limited to the use of hedgehog compounds that function in the subject methods equivalently to naturally occurring hedgehog polypeptides. The only remaining question then becomes whether the making and testing of hedgehog compounds constitutes undue experimentation. Applicants maintain the arguments of record in this regard, and contend that the experimentation required to make and test compounds at least 80% identical to the recited vertebrate hedgehog polypeptide is routine. The prior Office Action remarked that the "making and testing" is not the standard for evaluating the enablement of the claims. Applicants wish to clarify the arguments on this point. Applicants presented extensive evidence from both the art and the specification which demonstrate that the experimentation required to make and test variants of naturally occurring hedgehog polypeptide to identify hedgehog compounds which meet the limitations of the claims is routinely practiced. Accordingly, Applicants' arguments serve to demonstrate that, following the guidance provided by the disclosure and the state of the art, one of skill in the art could practice Applicants invention without undue experimentation.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of

whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. “The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). “Time and expense are merely factors in this consideration and are not the controlling factors.” *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

Applicants contend that the specification and the art provide extensive guidance such that one of skill could practice the claimed invention without undue experimentation. The level of skill in the art is very high, the specification provides extensive guidance concerning the functional and structural characteristics of the hedgehog compounds for use in the claimed methods, and the specification and the art provide extensive guidance concerning the making and testing of variant compounds. Applicants additionally point out that the claims are explicitly limited to hedgehog compounds which possess specific functional characteristics. Accordingly, following the guidance provided in the specification, one of skill in the art would have a reasonable expectation of success of generating hedgehog compounds that meet the limitation of the claims. Furthermore, one of skill in the art would expect to expend no more effort than is reasonably undertaken in the art to practice the invention.

The Office Action contends that predictability is required. It is true that the scope of enablement depends on the predictability of the relevant art. However, it is not required that the invention be restricted in scope to absolute black-and-white predictability. The test of enablement is whether one of skill in the art could practice the invention throughout its scope without undue experimentation – predictability and foreseeability are relevant only to the extent that undue experimentation is necessary to practice the full scope of the pending claims. Technology available at the time of filing, as has already been made of record, permits the preparation and testing of vast numbers of variant sequences with little or no human intervention whatsoever – the very essence of “routine experimentation.” The Office Action suggests that an “invitation to experiment” is not enough for patentability; however, if the invited experiments are merely routine, as here, no lack of enablement is present.

As pointed out above, claim 75, if pending, has been cancelled, thereby rendering rejection of this claim moot.

In summary, Applicants submit that the bulk of the evidence available in the literature both before the filing of the present application and thereafter supports the enablement of the pending claims, and that the references cited by the Examiner fail to apply to, no less to undermine, the enablement of the pending claims. Reconsideration and withdrawal of this rejection are respectfully requested.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully Submitted,



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